Vol. 40, No. 6, 1990

Drugs

Drugs is indexed in 'Current Contents', 'Index Medicus' and 'Excerpta Medica'

David J. Pinsky, et al.
Serial No. 08/721,447
Filed: September 27, 1996
Exhibit C

Drug Evaluation

Drugs 40 (6): 880-902, 1990
0012-6667/90/0012-0880/$11.50/0

DREND2 142

Transdermal Nitroglycerin (Glyceryl Trinitrate)
A Review of its Pharmacology and Therapeutic Use

Peter A. Todd, Karen L. Goa and *Heather D. Langtry*
Adis Drug Information Services, Auckland, New Zealand

Various sections of the manuscript reviewed by: ***J. Abrams***, Department of Medicine, School of Medicine, The University of New Mexico, Alberquerque, New Mexico, USA; ***E. Agabiti-Rosei***, Cattedra di Terapia Medica Systematica, Università di Brescia, Brescia, Italy; ***M. Bogaert***, Heymans Instituut voor Farmakodynamie en Terapie, Rijksuniversiteit, Gent, Belgium; ***J.N. Cohn***, Cardiovascular Division, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA; ***U. Elkayam***, Section of Cardiology, Department of Medicine, University of Southern California, Los Angeles, California, USA; ***R.J. Katz***, Division of Cardiology, Department of Medicine, The George Washington University, Washington, DC, USA; ***W. Rudolph***, Department of Cardiology, German Heart Center, Munich, Federal Republic of Germany; ***S. Scardi***, Centro Cardiovascolare, Ospedale Maggiore, Trieste, Italy; ***S. Scheidt***, Division of Cardiology, Department of Medicine, The New York Hospital, Cornell Medical Center, New York, New York, USA; ***N. Sharpe***, Department of Medicine, Auckland Hospital, Auckland, New Zealand; ***T. Takabatake***, First Department of Internal Medicine, Kanazawa University, Kanazawa, Japan.

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Synopsis

Nitroglycerin (glyceryl trinitrate) has been used for many years via the sublingual route for treating acute anginal attacks. In recent years transdermal delivery of nitroglycerin has gained popularity for prophylaxis against angina. However, nitrate tolerance appears to be a therapeutic problem with all long-acting nitrates regardless of delivery mechanism, and it occurs in most patients with stable angina treated with continuous 24-hour application of nitroglycerin patches. Since continuous 24-hour plasma concentrations of nitroglycerin do not appear to be desirable, alternative approaches to therapy are needed. A simple method to minimise tolerance with transdermal nitroglycerin patches is to remove the patch at bedtime and reapply a new patch in the morning. Such intermittent therapy allows a patch-free period during the night, when most patients experience few angina attacks, but optimises nitrate sensitivity during the daytime. However, the place of intermittent nitroglycerin patch therapy in the treatment of stable angina needs clarification with further study, particularly comparisons with other long-acting forms of nitrates. There are insufficient data to recommend the use of transdermal nitroglycerin patches in the treatment of patients with unstable angina or congestive heart failure.

In conclusion, transdermal nitroglycerin patches offer a convenient and cosmetically acceptable dosage form which has potential use in stable angina if administered as an intermittent regimen providing a patch-free period each night.

Pharmacological Profile

The numerous formulations of nitroglycerin patches, while using different technologies in their manufacture, essentially achieve the same pharmacological end-point at equivalent doses, i.e. the constant release of the drug across the skin into systemic circulation for 24 hours which achieves constant steady-state plasma concentrations of nitroglycerin.

The primary anti-ischaemic mechanism of action of nitroglycerin is believed to be relaxation of vascular smooth muscle. The biochemical events leading to vascular relaxation remain unknown, but are thought to include effects on cyclic guanosine monophosphate production to induce contractile protein relaxation, and the possibility that nitrates may be physiological substitutes for endothelium-derived relaxing factor (EDRF). Nonetheless, consequent vasodilatation leads to a reduction in preload and cardiac oxygen demand. A number of other mechanisms have been hypothesised, with recent evidence strongly suggesting an additional direct anti-ischaemic effect produced by improved coronary blood flow. In patients with congestive heart failure the higher doses that are generally used may produce a reduction in afterload from arteriolar dilatation, as well as the more important reduction in preload.

Systemic bioavailability of nitroglycerin is about 75 to 90% following patch administration. The drug is detected in plasma 30 to 60 minutes after application, steady-state plasma concentrations persist from 2 to 24 hours, and no drug is measurable in plasma within 1 hour of patch removal. Mean steady-state plasma concentrations are about 0.2 µg/L after a patch dose of 0.4 mg/h and are directly proportional to the dose administered. There may, however, be wide intra- and interindividual variation; up to 10-fold differences have been noted. This is probably related to the large volume of distribution (3 L/kg); plasma nitrate probably accounts for no more than 1% of the total body nitrate pool. The site of patch application does not affect absorption, but exercise or sauna may increase the rate of absorption from nitroglycerin patches. A phasic release nitroglycerin

patch has recently been developed which delivers about 75% of the dose in the first 12 hours and only 10 to 15% in the last 6 hours.

Metabolism of nitroglycerin is rapid (half-life of a few minutes): the action of glutathione-organic nitrate reductase yields 1- and 2-mononitrates, 1,2- and 1,3-dinitrates and glycerol which are mainly excreted renally. Relatively high dinitrate concentrations may be achieved in plasma and may contribute to the pharmacological activity of the drug.

Therapeutic Use

Controlled clinical trials of the continuous application of nitroglycerin patches throughout each 24-hour period indicate that tolerance may develop to the antianginal and anti-ischaemic effects of the drug in the majority of patients with stable angina. Attenuation of the response occurs as early as 8 to 12 hours after patch application, and opinion is divided whether any benefit is gained during long term continuous therapy. Therefore, as indicated by recent studies 'intermittent' therapy may provide a more rational approach to therapy. Removal of the patch for 10 to 12 hours in each 24-hour period provides a patch-free period which may allow the re-establishment of sensitivity to nitroglycerin. Use of a phasic-release nitroglycerin patch, which provides a 'nitrate-low' interval in each 24-hour period, may reduce the likelihood of developing tolerance. Comparisons with continuous patch application in fact do show improved maintenance of therapeutic effect with intermittent therapy. Longer term studies in larger numbers of patients are therefore required with 'intermittent' and phasic-release patch therapy to define more precisely the clinical efficacy of their anti-ischaemic and antianginal effects, in particular compared with other established long-acting nitrate treatments such as isosorbide dinitrate. In addition, with intermittent therapy a decreased exercise capacity to angina onset has been noted prior to patch application with long term treatment compared with placebo, raising the possibility of a rebound haemodynamic phenomenon. The clinical relevance of this observation is unknown. Until this has been investigated further, patients should be monitored carefully for any increase in angina frequency or severity during the patch-free period of intermittent therapy.

Studies of transdermal nitroglycerin in other therapeutic areas, including unstable angina and congestive heart failure, have been relatively few, but have generally indicated that continuous patch application is unlikely to be of use.

Adverse Effects

The adverse effect profile of nitroglycerin is well established and results from the drug's vasodilatory properties. Unwanted effects usually occur early in therapy and may disappear spontaneously or with a dosage reduction. They occur in about 20 to 30% of patients, leading to withdrawal in about 5 to 10% of patients. Headaches account for about three-quarters of all reported effects. This is followed less frequently by cutaneous reactions and postural hypotension (dizziness, weakness, rare syncope, and reflex tachycardia with occasional worsening of angina). Other adverse effects include bradycardia, flushing, nausea and vomiting. Cutaneous reactions usually involve mild erythema but may on occasions involve severe macular erythematous lesions usually related to the nitroglycerin itself and occasionally some component or excipient of the patch.

Dosage and Administration

The suggested starting dose of transdermal nitroglycerin in patients with angina is between 0.2 and 0.4 mg/h. Doses of between 0.4 and 0.8 mg/h have shown continued effectiveness for 10 to 12 hours/day for at least one month of intermittent administration. Although the minimum nitrate-free interval has not been defined, a nitrate-free interval of 10 to 12 hours in each 24-hour period, usually at night, limits the potential for tolerance. Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily 'patch-on' period of 12 to 14 hours and a daily 'patch-off' period of 10 to 12 hours.

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Nitroglycerin (glyceryl trinitrate) and other organic nitrates have been used in the treatment of angina for over 100 years. Sublingual nitroglycerin is still the most widely used treatment for the relief of acute anginal attacks. The drug is rapidly absorbed by this method, providing therapeutic blood concentrations and relief of angina within minutes. However, extensive metabolism leads to rapid clearance and therefore a short duration of action. Alternative methods of drug delivery were required to provide a longer duration of action suitable for prophylaxis against angina. One approach was the development of longer-acting nitrate esters such as the orally administered formulations of isosorbide dinitrate and 5-isosorbide mononitrate. Another was to devise dosage forms for nitroglycerin, such as sustained-release buccal and transdermal preparations, which provided more sustained therapeutic plasma nitrate concentrations. trations.

Transdermal nitroglycerin ointment was developed over 25 years ago and gained clinical acceptance during the 1970s following trials showing its prophylactic efficacy. Since it was reviewed in the Journal in 1982 (Elkayam & Aronow 1982) little information has been published on nitroglycerin ointment. It has proven inconvenient to use and required up to 4 daily applications, which led to poor patient compliance. Transdermal nitroglycerin patches were developed which were more convenient to use and administered once daily, thereby improving patient acceptability.

The present review therefore concentrates on the clinical use of once daily transdermal nitroglycerin patch delivery systems and includes a brief overview of their pharmacology. Many such devices have become available worldwide since the first nitroglycerin patches were developed in the early 1980s (Chien 1984; Olivari & Cohn 1983; Scheidt 1985). These have been variously called 'systems', 'films' or 'patches'. In this review the term 'patches' is used. Where appropriate, patch formulations are clearly distinguished by their brand names. Also, the generally accepted dose nomenclature is used, i.e. the amount of drug delivered per hour of application (e.g. 0.4 mg/h).

1. Pharmacology

1.1 Physical Composition and Characteristics of Nitroglycerin Patches

All patches have generally been designed with the same primary aim, which is to deliver nitroglycerin across the skin into the systemic circulation at a constant rate in order to maintain a steady-state concentration in the blood for up to 24 hours during a single application. Patches may deliver a higher rate after application (e.g. Deponit®) [Wolff et al. 1985], may have a fluctuating release rate (e.g. Biophase®) [Parker et al. 1989; Wolff & Bonn 1989], and are manufactured in different sizes to give various daily doses (Riedel et al. 1989).

There are many factors which confound the interpretation of bioavailability data and the determination of pharmacological equivalence for transdermal nitroglycerin products (see section 1.4 for discussion of pharmacokinetics). All patches with a constant-release profile generally perform similar functions. However, certain patches may be cosmetically more acceptable by patients and give better adhesion (De Ponti et al. 1989; Hay 1988; Noonan et al. 1986; Wick et al. 1989). Patches are composed of an impermeable backing on one side and a protective layer on the other side which is removed before application to the skin. There are, however, differences in the methods of adhesion to the skin and of containing the nitroglycerin within the patch. Nitrodisc® uses an adhesive rim around the edge of the contact pad and the nitroglycerin is contained within a matrix. Transderm® has a porous adhesive membrane with a nitroglycerin reservoir. In most systems (e.g. Biophase®, Deponit®; Nitro-Dur®, Minitran®), the nitroglycerin-containing matrix acts concomitantly as the adhesive layer. The amount of nitroglycerin within the patch far exceeds the amount that is delivered over 24 hours (Chien 1984; De Ponti et al. 1989; Noonan et al. 1986; Wolff & Bonn 1989; Wolff et al. 1985).

1.2 Mechanism of Action

Several reviews have examined the biochemical mechanisms proposed to explain the mode of action and development of tolerance to organic ni-

trates at a cellular level (Ahlner & Axelsson 1987; Axelsson & Ahlner 1987; Flaherty 1989; Fung et al. 1989; Silber 1990). A précis based on these reviews is presented here with the addition of some recently published data.

Induction of relaxation of vascular smooth muscle is the common primary mechanism of action proposed to explain the pharmacological effects of all organic nitrates (nitro esters), for which nitroglycerin may be considered a prototype. Nitrates enter the smooth muscle cell possibly via the postulated 'nitrate receptor', although this has yet to be fully characterised. Inside the cell, nitrates may react with sulfhydryl groups leading to the formation of disulphides and short-lived intermediates called *S*-nitrosothiols. The latter are believed to interact with the haem moiety of the enzyme guanylate cyclase either directly or indirectly by liberating nitric oxide. Stimulation of guanylate cyclase increases cyclic guanosine monophosphate (cGMP) production in vascular smooth muscle cells, which in turn lowers cytosolic free calcium concentrations by unknown mechanisms. Nonetheless, this reduction in cytosolic calcium directly leads to a relaxation of contractile proteins and vasodilatation.

Although considerable controversy exists, a number of investigators consider endothelium-derived relaxing factor (EDRF) to be indistinguishable from nitric oxide (for example, Palmer et al. 1987). The absence or dysfunction of endothelium in atherosclerotic coronary vessels may allow inappropriate vasoconstriction because of a lack of EDRF counter-regulation. Nitrates might therefore be considered as physiological substitutes for EDRF, an 'endogenous nitrate' (Silber 1990).

Various other factors have been suggested as playing a possible role in the mechanism of action of nitrates. Primarily based on experimental *in vitro* and animal studies, it has been hypothesised that nitrates may interact with the prostaglandin pathway, for example by increasing prostacyclin levels in vascular tissues. Nitroglycerin may also inhibit platelet aggregation (Stamler et al. 1989). Nitrates, and nitroglycerin patches (Brügger et al. 1985; Pedrinelli et al. 1989) in particular, improve blood rheology, with significant decreases in blood viscosity and haematocrit. Nitroglycerin may [illegible] cause oxygen to dissociate more easily from [illegible] haemoglobin and thus become more readily [illegible] able to the myocardium (Osnes 1987). However, the clinical relevance of these findings is unclear.

Several hypotheses have been proposed [illegible] might explain the development of nitrate tolerance at a cellular level. These have included [illegible] creased distribution of nitrate to vascular [illegible] muscle cells, as well as reduced activity of [illegible] late cyclase leading to decreased production [illegible] increased degradation of cGMP. However, the 'sulfhydryl depletion hypothesis' has received the most attention. This postulate holds that the depletion of critical sulfhydryl groups at the 'nitrate receptor' during continued nitrate exposure leads to reduced production of *S*-nitrosothiol, the [illegible] cellular intermediate necessary to stimulate guanylate cyclase and cause cellular relaxation. [illegible] *in vitro* and *in vivo* experiments show that [illegible] tolerance may be reversed using sulfhydryl [illegible] (such as *N*-acetylcysteine, captopril and [illegible] nine) [Levy et al. 1989; Neuberg et al. 1989]. However, this has not been the case in clinical [illegible] (Hogan et al. 1989; Parker et al. 1987).

1.3 Haemodynamic Effects

The pharmacodynamic effects of nitrates, and nitroglycerin in particular, have been thoroughly discussed in previous reviews (Abrams 1983, 1988; Brown et al. 1984; Elkayam & Aronow 1982; Flaherty 1989; Frishman 1985; Olivari & Cohn 1983). These effects are briefly summarised here.

1.3.1 Angina Pectoris

In patients with angina pectoris, nitroglycerin acts by a combination of direct and indirect effects on preload and afterload as well as on coronary circulation. Venodilatation occurs at low nitrate concentrations, whereas arterial and arteriolar dilatation occur preferentially at high concentrations. This selective dilatation of venous capacitance vessels produces a reduction in preload, which decreases right and left ventricular pressures during

diastole, thereby reducing right atrial, pulmonary capillary wedge and pulmonary artery diastolic pressures. As a consequence, ventricular cavity size, wall tension and cardiac oxygen demands are reduced. Blood flow to the deeper layers of the myocardium may increase as intramural pressure on the subendocardial vessels falls during diastole. Nitrate-induced dilatation of coronary artery stenosis will produce a large increase in coronary flow. A favourable redistribution of flow from nonischaemic to ischaemic areas may result from an increase in intercoronary collateral flow. Coronary vasospasm occurring at rest and during exercise can be relieved by nitroglycerin.

The end result of these actions is improved myocardial oxygen supply to ischaemic areas. The relative importance of the different mechanisms will vary depending on the dose of nitroglycerin administered, the severity of the coronary disease, the underlying peripheral and coronary vascular tone, presence or absence of ventricular dysfunction, concomitant use of other anti-ischaemic drugs, etc. Thus, considerable interindividual variation in response can occur. A more detailed discussion of the short and longer term haemodynamic and clinical effects in patients with angina pectoris is given in section 2.

1.3.2 Congestive Heart Failure

In congestive heart failure, the clinical benefits of nitrates appear to result, at least in part, from dilatation of venous capacitance vessels, thereby reducing filling pressures and preload in both the left and right sides of the heart. At the higher nitrate doses generally used in congestive heart failure, arteriolar dilating properties may also contribute by decreasing aortic impedance and thus increasing stroke volume, despite the preload reduction.

There have been many studies which have examined the short term haemodynamic effects of a single transdermal application of nitroglycerin in patients with congestive heart failure (Armstrong 1987; Elkayam et al. 1985; Ino-Oka et al. 1989; Jordan et al. 1985, 1986; Olivari et al. 1983; Packer et al. 1986; Pfister & Noseda 1982; Rajfer et al. 1984; Roth et al. 1987; Sharpe & Coxon 1984; Sharpe et al. 1987; Vogt & Kreuzer 1986). These studies have rarely included a placebo control and usually included small numbers of patients (about 10 on average). Background medication varied greatly between patients. In some studies, 'nitrate-responders' were preselected before the trial, since it is known that some patients (perhaps 10 to 15%) [Packer et al. 1986] do not show a response to any nitrate preparation. In addition, a wide range of doses were studied from 0.2 (Sharpe & Coxon 1984) to as high as 5 mg/h (Roth et al. 1987), although doses have usually been 1.6 to 3.6 mg/h which is considerably higher than that normally used in patients with angina.

Invasive haemodynamic monitoring in these studies documented improvement (increased cardiac index, and decreased systemic vascular resistance, right atrial pressure and pulmonary capillary wedge pressure without any change in heart rate or mean arterial pressure) which started about 1 hour after patch application and reached a maximum after about 2 to 6 hours. However, there was a rapid attenuation of the response and a loss of effect within 8 to 12 hours from application in the majority of patients. Thus, in these single-dose studies of transdermal nitroglycerin, patients rapidly developed tolerance.

1.3.3 Tolerance

It is important to bear in mind that the haemodynamic effects of nitroglycerin during short and long term use in patients with angina or congestive heart failure can be attenuated or negated by the development of nitrate tolerance (see section 2). An example of the attenuation of effect in congestive heart failure is shown in figure 1. A statistically significant reduction in pulmonary capillary wedge pressure was only seen from 2 to 12 hours when compared with placebo.

As mentioned above (section 1.2), the development of nitrate tolerance may occur at a cellular level. It has also been hypothesised that various counter-regulatory vasoconstrictor mechanisms, such as reflex sympathetic activation and more particularly stimulation of the renin-angiotensin

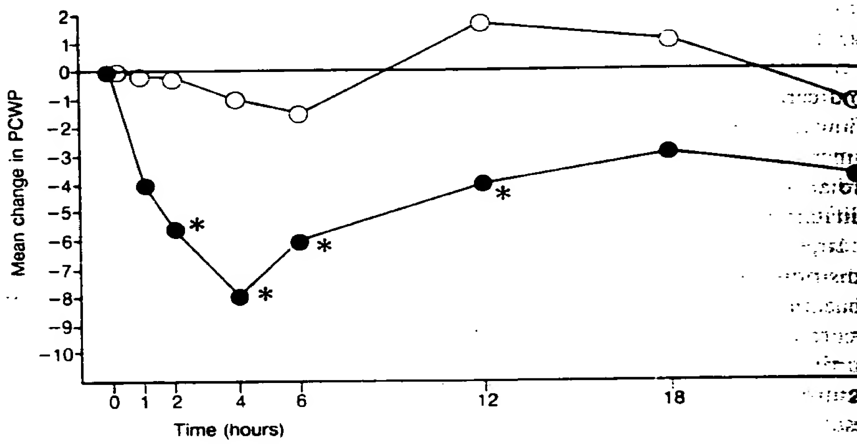

Fig. 1. Change in mean pulmonary capillary wedge pressure (PCWP) in patients with congestive heart failure [illegible] single transdermal application of nitroglycerin 2.4 mg/h for 24 hours (●, n = 8) or placebo (○, n = 7). * = [illegible] significant ($p < 0.05$) difference between treatments (after Jordan et al. 1985).

system, may play a role in tolerance development (Flaherty 1989; Silber 1990). Indeed, cellular and counteractive vasoconstrictor mechanisms may play differential roles in the development of nitrate tolerance after single doses and longer term use. As noted by Fung et al. (1989), no single hypothesis is consistent with all available data and *in vivo* tolerance may involve varying combinations of the different mechanisms proposed.

1.4 Pharmacokinetics

The pharmacokinetics of nitroglycerin following the use of systemic and transdermal preparations have recently been reviewed (Bogaert 1987). It is only within the past decade that highly sensitive and specific analytical techniques have been developed for the determination of nitroglycerin concentrations in plasma. These were described by Bogaert (1987): gas chromatography in combination with electron capture detection or mass spectrometry are the commonest methods used. Although the metabolites of nitroglycerin (glyceryl dinitrates and mononitrates) are present in significant quantities in plasma and the dinitrates possess significant pharmacological activity, little information is available on their analysis [illegible]tion in plasma. However, Jaeger et al. ([illegible]) developed a sensitive and specific gas [illegible]graphy/electron capture detection technique [illegible] determination of glyceryl 1,3-dinitrate [illegible] 1,2-dinitrate in plasma.

The elimination half-life of nitroglycerin [illegible]ministered orally was reported as 1 to 3 [illegible] (Olivari & Cohn 1983). However, first pass through the liver appears not to allow any parent drug into the systemic circulation: Yu et al. (1988) reported nitroglycerin in plasma only up to 1 hour after oral ingestion of 9 or 13mg. Thus, only transient plasma concentrations are achieved during oral administration. By providing a constant rate of drug delivery to systemic circulation, transdermal patches achieve continuous plasma concentrations.

Despite differences in the design of nitroglycerin patches, they generally release the drug at a constant *in vivo* rate of 0.02 mg/cm^2/h, which closely corresponds with the *in vitro* release rate (Bogaert 1987). This *in vivo* rate is based on estimates made by measuring residual levels in patches after wear. The phasic release patch (Biophase[illegible]) differs from conventional patches since it delivers about 75% of the dose in the first 12 hours, and

only about 10 to 15% in the last 6 hours (Bergbauer & Weber 1989; Knapp & Turpe 1989; Parker 1989; Schirnick & Reifart 1989; Wolff & Bonn 1989).

Various *in vitro* dissolution models have been used to determine the release rate of nitroglycerin from patches (Aiache et al. 1989; Pirotte & Jaminet 1984; Shah et al. 1986, 1988). The rate of transdermal delivery of nitroglycerin has been quantified *ex vivo* across animal and human skin and *in vivo* by back extrapolation from pharmacokinetic data (Chien 1984): the 2 methods show good correlation although there is some question regarding the reliability of the back extrapolation method. Patch dose may be conveniently expressed as the amount of nitroglycerin delivered from the patch over 1 hour (in mg/h) and can be determined from the amount of drug lost from the patch in this time after human application. Patches are worn for 24 hours and the data are time-averaged. This method allows comparisons of pharmacokinetics between different brands of patch.

Not all of the drug released from the patch reaches the systemic circulation. Compared with intravenous administration, 75 to 90% of nitroglycerin was systemically bioavailable following patch administration (Imhof et al. 1984; Isenschmid et al. 1985; Riess et al. 1985). The lost drug may be accounted for by retention at the application site, tissue binding and breakdown (Imhof et al. 1984).

Many studies have examined the plasma concentrations of nitroglycerin after patch administration (e.g. Chu et al. 1984; Curry et al. 1984a,b; De Ponti et al. 1989; Gerardin et al. 1985; Heidemann et al. 1985; Imhof et al. 1984; McAllister et al. 1986; Müller et al. 1982; Noonan et al. 1986; Wolff et al. 1985). Most studies involved healthy subjects. Despite the lack of direct comparisons, similar results were achieved in patients with angina or congestive heart failure. Nitroglycerin was detected in plasma 30 to 60 minutes after patch application, steady-state was maintained from 2 to 24 hours, and no drug was measurable within 1 hour of patch removal (fig. 2). Mean steady-state concentrations were generally about 0.2 μg/L following a patch dose of 0.4 mg/h. In addition, mean steady-state concentrations were directly proportional to the dose whether administered as a single or several patches (Imhof et al. 1984; Müller et al. 1982; Riedel et al. 1989), and were maintained during repeated daily applications up to 10 days (Müller et al. 1982).

The above are general findings. Some studies have shown considerable differences in pharmacokinetic values, which may be related to the analytical techniques used but could also be ascribed to the complexity of nitroglycerin pharmacokinetics. Considerable intra- and intersubject variation occurs in steady-state plasma concentrations of nitroglycerin, with up to 10-fold differences within individual studies (Curry et al. 1984b; Gerardin et al. 1985; Müller et al. 1982; Noonan et al. 1986; Reiniger et al. 1987). Indeed, McNiff et al. (1981) reported that steady-state nitroglycerin concentrations were not established even after continuous intravenous infusion. Although the degree of patch adhesion to skin may contribute slightly to this variability, it is most probably related to the large (3 L/kg) volume of distribution of nitroglycerin and large total body clearance values (1800 to 2400 L/h) [Wolff et al. 1985]. Plasma nitrate may reflect no more than 1% of the total body nitrate pool (McNiff et al. 1981); thus, small distributional shifts in the peripheral compartment may produce large changes in plasma concentration.

Comparisons of different brands of patches at the same dose have not usually shown significant differences in mean steady-state plasma concentrations of nitroglycerin. However, studies included only small numbers of subjects and did not evaluate differences in rates of absorption between patches. No differences were found between Nitrodisc® and Transderm-Nitro® (Chien 1984; McAllister et al. 1986), and between Adestrin® (equivalent to Deponit®), Nitroderm® and Nitro-Dur® in 12 subjects (De Ponti et al. 1989). In the latter study, Nitro-Dur® produced a greater fluctuation in steady-state plasma concentrations (double that of the other products, $p < 0.05$), but only 10 of the 12 subjects received this formulation whereas all subjects received the other two. Heidemann et al. (1985) found comparable plasma concentrations with Nitrodisc® and Nitroderm®,

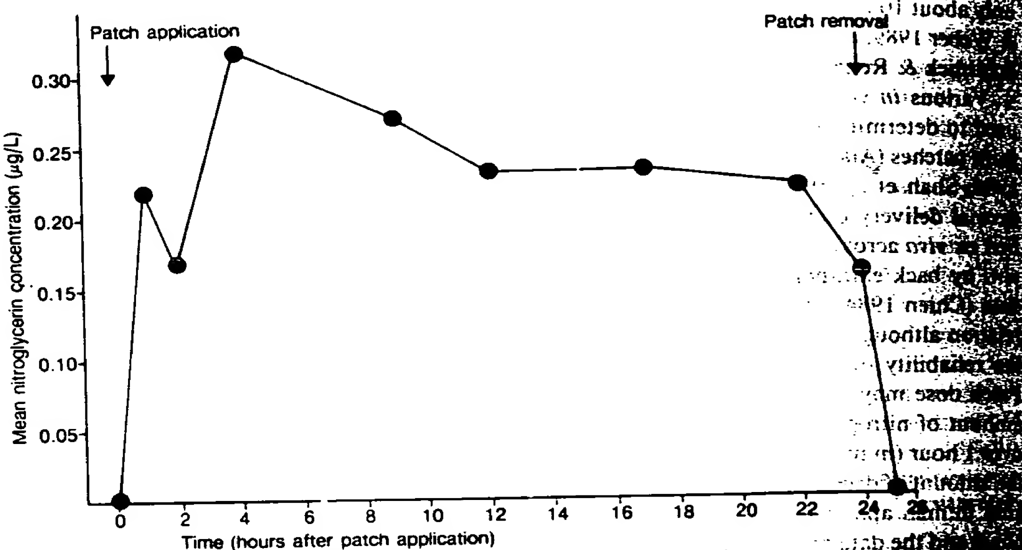

Fig. 2. Mean nitroglycerin plasma concentrations after application of a 0.4 mg/h patch in 11 healthy volun[illegible] et al. 1984a).

but significantly lower concentrations with Deponit® and Nitro-Pflaster-ratiopharm®. Wolff et al. (1985) showed that the plasma profile of nitroglycerin had a peak at 2 hours after application of a Deponit® patch which was about twice as high as the steady-state concentration from 8 to 24 hours.

The site of patch application (chest, upper arm and hip) did not significantly affect the plasma concentration of nitroglycerin (Gerardin et al. 1985) or its pharmacological activity (Hamer et al. 1983). The rate of drug release is determined by the patch itself and is largely unaffected by skin characteristics (Chien 1984; Scheidt 1985). Also, plasma concentrations were not significantly affected by patch application when the subject was supine or standing (Heidemann et al. 1987). Mean steady-state plasma concentrations were increased at least 2-fold (Barkve et al. 1986; Weber et al. 1987), and as much as 6-fold (Lefebvre et al. 1990) during exercise compared with the resting state and about 5-fold during sauna (Barkve et al. 1986). This is presumed to be caused by increased nitroglycerin uptake because of vasodilatation. The relationship between plasma nitroglycerin concentrations and pharmacological effects is contro[illegible] correlation has been established (B[illegible] Zeller & Klamerus 1987).

Nitroglycerin undergoes rapid meta[illegible] glutathione-organic nitrate reductase [illegible] smooth muscle, erythrocytes and in the liver (Armstrong et al. 1980; Fung et al. 1984; Needleman et al. 1971, 1972). Since nitroglycerin has a half-life of only a few minutes in blood (Bennet et al. 1985; Cossum & Roberts 1982), rapid loss of drug in blood samples can occur unless they are quickly collected and centrifuged cold. This may have affected the determination of nitroglycerin in some studies. The total body clearance of nitroglycerin after patch administration was about 1800 to 2400 L/h (Chu et al. 1984; Gerardin et al. 1985; Wolff et al. 1985). Metabolism of nitroglycerin yields 1- and 2-mononitrates, 1,2- and 1,3-dinitrates, and glycerol, which are mainly excreted renally (Kampmann 1987). Jaeger et al. (1987) found that steady-state plasma concentrations of glyceryl 1,2-dinitrate and glyceryl 1,3-dinitrate were about 10- and 5-fold higher, respectively, than that of nitroglycerin about 4 hours after patch application to healthy

volunteers. Although the vasodilating effect of the metabolites is considerably less than that of nitroglycerin on a weight-for-weight basis (for review see Curry & Aburawi 1985), it is possible that they may contribute to the overall effect by being present in relatively high concentrations.

2. *Therapeutic Use in Stable Angina*

The use of nitroglycerin patches has been most extensively investigated in patients with stable angina. There have been relatively few studies comparing different, clearly specified formulations of nitroglycerin patches with respect to clinical efficacy or acceptability. Generally, there has been little indication of differences in clinical effectiveness based on anginal attack frequency and sublingual nitroglycerin consumption, which might be expected in view of the similar drug release characteristics of the formulations. Cronin et al. (1987) found that Nitrodisc® and Transderm-Nitro® had the same clinical efficacy, although the latter was preferred ($p < 0.005$) mainly for its cosmetic and adhesive properties. Vallé-Jones et al. (1989) noted that Deponit® and Transderm-Nitro® were equally acceptable cosmetically, while in terms of efficacy the former was significantly preferred to the latter. Minitran® has been shown to be preferred over Transderm-Nitro® and Nitro-Dur®, mainly for cosmetic and adhesive properties (Hougham et al. 1989; Wick et al. 1989).

2.1 Continuous Use

2.1.1 Placebo-Controlled Studies

As early as 1980 it was noted that multiple daily doses of orally administered nitrates, leading to plasma concentrations continuously within the therapeutic range, were invariably associated with tolerance development (Rudolph et al. 1981). Since that time there has been much controversy over the degree of tolerance development which occurs and is independent of the mode of nitrate administration (for reviews see Abrams 1988; Charash & Scheidt 1986; Flaherty 1989; Frishman 1985; Scheidt 1985; Zeller & Klamerus 1987). However, it has become increasingly evident and generally accepted that tolerance will be a clinical problem in the majority of patients with stable angina treated with continuous transdermal nitroglycerin patches throughout 24 hours. Preliminary results are available from a double-blind placebo-controlled multicentre trial of over 500 patients with stable angina treated with a range of patch brands with doses ranging from 0.6 to 4.2 mg/h (Abrams 1989). Beneficial antianginal effects occurred only at the 4-hour post-patch exercise test on the first day of therapy but were lost in all treatment groups during long term use. No improvement in exercise parameters was found at any dose level after 8 weeks of daily administration.

Prior to this study, numerous placebo-controlled trials had been performed which were repeatedly reviewed with various conclusions concerning the degree of the clinical significance of tolerance (for references of reviews see above). Some attention will be paid to the design of these clinical trials but it is not intended to give complete details.

Most trials were double-blind and involved small numbers (usually 5 to 25) of patients, limiting the statistical power to show differences between treatments. The placebo response to patches in particular may be high in patients with angina. Maintenance of double-blind conditions may be difficult because many patients are familiar with the characteristic adverse effects of nitrates. Both short term (up to 24 hours) and longer term (usually greater than 1 week) effects have been studied; however, relatively few of the longer trials lasted beyond 1 to 2 weeks (e.g. Gibelli et al. 1989; Martines 1984; Rehnqvist et al. 1986). Disease severity, concomitant medications, nitroglycerin dosage and therapeutic end-points also varied. Effectiveness was evaluated using measures which were subjective (attack frequency or sublingual nitroglycerin consumption) or objective (such as treadmill performance, bicycle ergometry, capacity for or duration of exercise to angina onset, or Holter monitoring). Seardi et al. (1988) demonstrated a dissociation between haemodynamic and ergometric responses, as well as variation in interindiv-

idual responses. to continuous transdermal nitroglycerin therapy. Wide interindividual response (from no response to a significant response) was also stressed by Muiesan et al. (1986). Most studies assessed tolerance by the attenuation or disappearance of clinical effectiveness after single or multiple doses.

24-Hour studies have generally shown that the maximum response occurred about 3 to 6 hours after patch application. Relatively few studies have shown full maintenance of this effect for 24 hours (e.g. Ollivier et al. 1987; Scardi et al. 1985; Schiavoni et al. 1982; Sellier et al. 1985; Thompson 1986; Wiechman 1985). Most often, there has been an attenuation of the response starting at 8 to 12 hours after application, which has frequently led to a complete loss of efficacy at 24 hours (e.g. Cerri et al. 1984; Crean et al. 1984; Frishman et al. 1989; Gibelli et al. 1989; Heepe 1987; James et al. 1985; Parker & Fung 1984; Reichek et al. 1984; Reiniger et al. 1985; Schneider et al. 1985; Thadani et al. 1986). When examined in either short term or longer term studies, a dose-related response to nitroglycerin patches was not generally apparent (e.g. Cerri et al. 1984; Parker & Fung 1984; Reiniger et al. 1985; Scardi et al. 1985; Schneider et al. 1985; Thadani et al. 1986).

Long term studies have also shown a divergence of opinion as to whether tolerance develops. Often there has been a complete loss of response at 24 hours after the dose with treatment for 1 to 4 weeks (e.g. Crean et al. 1984; Frishman et al. 1989; Gibelli et al. 1989; Jackson et al. 1984; Khurmi et al. 1986; Nicholls et al. 1986; Parker & Fung 1984), but a clinically relevant response has also occurred (e.g. Dickstein & Knutsen 1985; Georgopoulos et al. 1982; Imhof et al. 1985; Martines 1984; Muiesan et al. 1986; Rezaković et al. 1986, 1988; Terland & Eidsaunet 1986; Thompson 1986). However, even in the latter studies some attenuation of the maximal short term response at about 3 to 6 hours after administration was seen during long term therapy. Other reviews have discussed these discrepancies (Charash & Scheidt 1986; Flaherty 1989; Scheidt 1985; Zeller & Klamerus 1987).

2.1.2 Comparisons with Other Agents [illegible]

There have been relatively few studies [illegible] ing continuous use of nitroglycerin [illegible] other treatments in patients with stable [illegible] These have generally had the same method[illegible] problems as those which have been [illegible] placebo-controlled studies (see section [illegible] Available results have been conflicting [illegible] allow definitive conclusions to be drawn.

Two double-blind 2-week studies [illegible] pared nitroglycerin patches with other [illegible] nitroglycerin preparations in patients [illegible] who had been withdrawn from previo[illegible] lactic antianginal medication. In a cross[illegible] in 12 patients, Weisbort et al. (1986) found [illegible] single nitroglycerin patch of 0.2 mg/h [illegible] exercise test parameters significantly [illegible] tenuation at 24 hours on the first and [illegible] treatment, whereas an orally administ[illegible] tained release formulation of nitrogly[illegible] twice daily produced no improvement [illegible] However, in a parallel study in 41 patie[illegible] et al. 1986) transdermal nitroglycerin [illegible] failed to produce any first-dose or [illegible] sponse, whereas buccal sustained release [illegible] erin 5mg 3 times daily produced a [illegible] provement in exercise parameters after [illegible] dose, an effect which was not attenuated during the longer term.

It was suggested by Osterspey et al. (1984) in a single-dose study that 5-isosorbide mononitrate 20mg was more effective than 2, but less effective than 4, patches of nitroglycerin 0.2 mg/h with respect to haemodynamic response and antianginal efficacy. In a randomised, nonblind crossover study in 13 patients (Löllgen et al. 1984) 2 weeks' treatment with 5-isosorbide mononitrate 20mg 3 times daily and transdermal nitroglycerin 0.2 mg/h were similarly effective.

Similarly, comparisons of nitroglycerin patches with isosorbide dinitrate have failed to establish their relative efficacies. Single doses of transdermal nitroglycerin 0.4 mg/h and sustained release isosorbide dinitrate 20mg produced similar improvement in exercise test parameters 4 hours after administration in 9 patients (Colombo et al. 1985).

In a multicentre study in 74 patients (Auer 1986), transdermal nitroglycerin 0.2 to 0.4 mg/h and sustained release isosorbide dinitrate 40 to 80mg twice daily proved therapeutically equivalent. However, Nicholls et al. (1986) demonstrated that conventional isosorbide dinitrate 10mg 3 times daily was therapeutically effective in 20 patients, whereas a nitroglycerin 0.2 mg/h patch showed no effect. It should be noted that the 0.2 mg/h patch dose is at the low end of the suggested dosage range. Conversely, two other studies in 10 (Imhof et al. 1985) and 51 (Letzel et al. 1982) patients found that transdermal nitroglycerin 0.2 to 0.4 mg/h was more effective than sustained release isosorbide dinitrate 40 to 80mg twice daily.

Transdermal nitroglycerin 0.2 mg/h and nifedipine 20mg twice daily for 2 weeks each reduced the number of anginal attacks and sublingual nitroglycerin capsules consumed in a crossover study in 12 patients (Wester & Mouselinis 1984). More recently, Shell and Dobson (1990) compared nifedipine 10mg 3 times daily and transdermal nitroglycerin 0.6 mg/h in a 2-week, crossover, double-blind study in 20 patients using treadmill exercise testing and 24-hour ambulatory Holter monitoring as end-points. With transdermal nitroglycerin the duration of ischaemia decreased by 57% (from 140 to 60 min/24h, $p = 0.005$), while there was a nonsignificant increase in exercise time of 5.5% (from 4.8 to 5.0 min, $p = 0.16$). With nifedipine the duration of ischaemia decreased nonsignificantly by 22% (175 to 137 min/24h, $p = 0.16$), but exercise time increased by 13% (from 4.5 to 5 min, $p = 0.026$). These results confirmed that exercise time changes do not necessarily reflect changes in total ischaemia duration.

2.1.3 General Practice Studies

There have been a number of general practice or postmarketing surveillance studies involving many thousands of patients treated for up to 3 months with low doses (0.2 to 0.4 mg/h) of different brands of nitroglycerin patches (Agabiti Rosei et al. 1987; Bridgman et al. 1984; Düsing & Juergens 1987; Letzel & Johnson 1983, 1984; Scheiner et al. 1988; Strano et al. 1990; Tattersall et al. 1985).

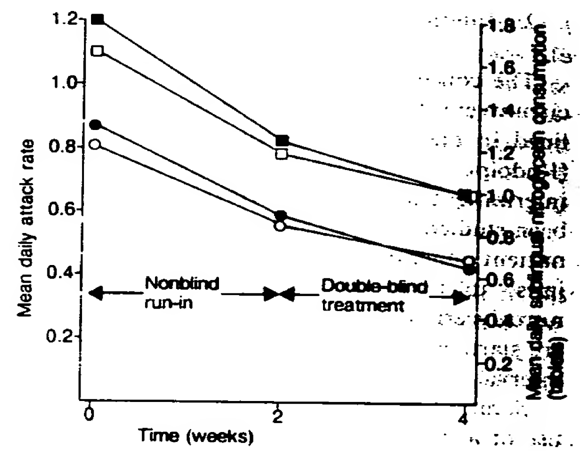

Fig. 3. Mean daily anginal attack rate (■, □) and sublingual nitroglycerin consumption (●, ○) in 427 patients randomised to receive transdermal nitroglycerin 0.2 mg/h (closed symbols) or placebo (open symbols) for 2 weeks after a 2-week run-in on no treatment (after Fletcher et al. 1988).

These studies can provide useful data on tolerability (section 4). However, because of their noncomparative design and lack of controls to reduce bias the apparently impressive response rates, ranging from about 75 to 90% of patients showing a reduction in anginal attack frequency, must be viewed with caution. The placebo response to transdermal nitroglycerin patches may be very high. Indeed, in a randomised, placebo-controlled, double-blind, general practice study in a large number of patients (427), there was no statistically significant difference between transdermal nitroglycerin 0.2 mg/h (the lowest suggested dose) and placebo after 2 weeks' treatment (Fletcher et al. 1988) when assessed for anginal attack rate or sublingual nitroglycerin use (fig. 3): both the placebo and actively treated groups showed a strong response during the 2-week nonblind run-in as well as during the 2-week double-blind phase. The same authors (Fletcher & Bulpitt 1988) also noted no difference in efficacy between transdermal nitroglycerin 0.2 and 0.4 mg/h in a randomised, double-blind, 2-week trial in 436 patients, although no placebo group was included.

2.2 Intermittent Use

The concept of intermittent nitrate therapy to circumvent the problem of tolerance was first outlined in the early 1980s for isosorbide dinitrate (Rudolph et al. 1983) and since the mid 1980s the intermittent use of transdermal nitroglycerin has been studied. As early indications were that intermittent rather than continuous therapy might minimise tolerance, manufacturers of conventional nitroglycerin patches with flat drug release profiles are starting to recommend the use of a patch-free interval.

Some of the initially published results on the use of a patch-free interval were not particularly encouraging (Reiniger & Rudolph 1985). 10 patients were studied on 3 separate days: a 0.6 mg/h patch was applied on the first day, renewed on the second day, and renewed on the third day after a 10-hour patch-free interval in the night. Exercise testing revealed a significant response for up to 14 hours after the first dose with a rapid attenuation by the end of 24 hours. During the second continuous dose the short term responses were markedly attenuated. Repeated testing on the third dose after a 10-hour patch-free interval showed no response to the patch, indicating that tolerance remained. However, in a subsequent study by the same group (Reiniger et al. 1987), the results with intermittent therapy were more promising. A lower dose of 0.4 mg/h was used in a double-blind, crossover, placebo-controlled study in 10 patients. Exercise testing revealed a similar response to patch application during 12 hours after the first dose was applied and after application of the second dose following a 12-hour patch-free interval. When the second dose was left in place for 24 hours and immediately followed by the third dose the acute exercise response was markedly attenuated compared with the first and second doses. The authors concluded that the positive results in the latter study compared with the former were caused by the use of a lower dose and a longer patch-free interval.

Cowan et al. (1987) compared continuous with intermittent nitroglycerin 0.4 mg/h (12 hours patch-free at night) therapy for 7 days in a double-blind, crossover, placebo-controlled trial in 12 [illegible] with stable angina. During continuous [illegible] beneficial effects on exercise time and ST [illegible] sion during the first dose were lost during [illegible] therapy, whereas they were fully maint[illegible] intermittent therapy. Both intermittent [illegible] tinuous therapy had no effect on noct[illegible] frequency compared with placebo, but [illegible] therapy appeared more effective than [illegible] therapy in reducing the diurnal angina [illegible] and sublingual nitroglycerin consumption [illegible] for the latter). Using a virtually identical [illegible] but with an 8-hour patch-free interval [illegible] mittent therapy, Luke et al. (1987) noted [illegible] results in 12 patients, i.e. the acute [illegible] sponse was abolished after 1 week with [illegible] therapy, but was maintained during [illegible] therapy. In a placebo-controlled cross[illegible] (Schaer et al. 1988) in 13 patients, the [illegible] sponse on exercise testing on the first day [illegible] with transdermal nitroglycerin 0.4 to [illegible] trated to maximum response was main[illegible] 1 week when a patch-free interval of [illegible] night was employed.

Waters et al. (1989) compared conti[illegible] 2 intermittent regimens (6 and 10 hours [illegible]) of nitroglycerin 0.4 mg/h in a placebo-controlled crossover trial in 36 patients. Exercise tests were performed during the last 2 hours of patch application. Compared with placebo, none of the 3 regimens prolonged total exercise time or time to 1mm ST depression after 3 days' treatment. There was, however, a significant increase in time to angina (40 sec, p = 0.001) with the 10-hour patch-free regimen.

Unlike previous studies where patients almost invariably received long-standing concomitant medication with β-blockers and/or calcium antagonists, 2 studies have compared continuous and intermittent (with a 12-hour patch-free period at night) nitroglycerin as monotherapy in a placebo-controlled, double-blind, crossover design. Using treadmill exercise testing Ferratini et al. (1989) found a statistically significant greater increase in exercise duration and time to onset of ST-segment depression during intermittent compared with con-

tinuous therapy at a dosage of 0.8 mg/h in 10 patients. However, overall angina frequency appeared similar with both treatments, although daytime angina frequency was higher with continuous therapy ($p < 0.01$) and night-time frequency was higher with intermittent therapy ($p < 0.05$). Nabel et al. (1989) compared maximally tolerated doses of transdermal nitroglycerin 1.2 to 2.4 mg/h as continuous and intermittent doses for 3 days in 14 patients using ambulatory ECG monitoring. Both treatment regimens produced an initial beneficial reduction in the frequency and duration of ischaemia, but this benefit was lost within 48 hours after the onset of either continuous or intermittent therapy.

DeMots and Glasser (1989) have reported a large scale, double-blind parallel study in 206 patients comparing intermittent (12-hour patch-free period at night) nitroglycerin 0.2 to 0.4 and 0.6 to 0.8 mg/h and placebo for 4 weeks. Figure 4 shows the results of exercise testing on the first and last day of treatment. Compared with placebo both actively treated groups increased the time to angina onset during the 12 hours after application of the first dose, and this was statistically significant at most time points and appeared dose related. After 4 weeks' treatment some attenuation appeared to have occurred: the group treated with a lower dose no longer exhibited statistically significant differences compared with placebo and the group treated with a higher dose only showed a difference at 8 hours. There were no differences between the 3 groups with respect to anginal frequency or sublingual nitroglycerin consumption.

A potentially important observation, which has not been previously noted, was a decreased capacity to exercise to angina development in the groups actively treated when tested just prior to patch application, compared with placebo after 2 and 4 weeks' treatment. Nine patients, all of whom had been actively treated, experienced a significant increase in nonexertional angina during the patch-free period, but completed the study uneventfully. Clearly, patients should be carefully monitored for any increase in angina frequency or severity during the patch-free period. Headache occurred in 61 to 70% of the actively treated patients and was sufficiently severe to necessitate treatment withdrawal in 6 patients.

de Milliano et al. (1989) compared placebo and

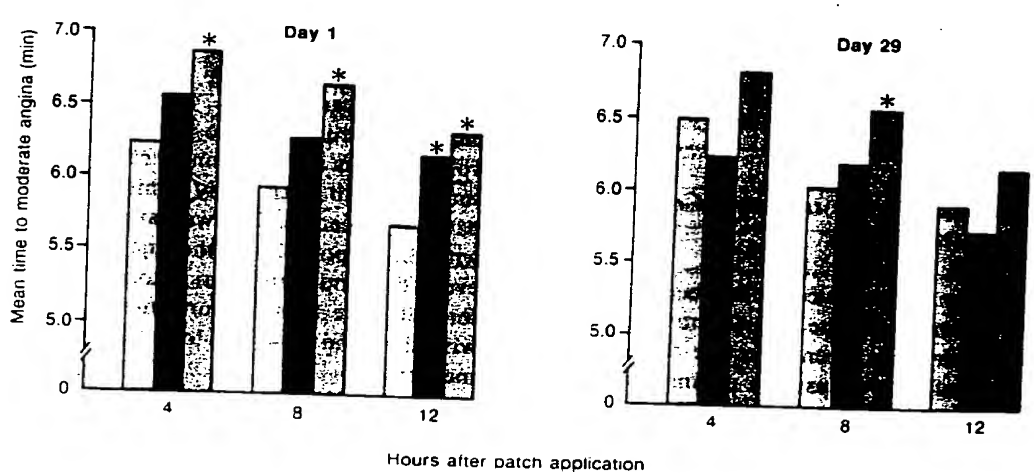

Fig. 4. Mean time to the development of moderate angina on a treadmill exercise test in 206 angina patients randomised to receive intermittent therapy with nitroglycerin patches 0.2 to 0.4 mg/h (■), 0.6 to 0.8 mg/h (▨) and placebo (□) for 4 weeks. * = statistically significant difference ($p < 0.05$) from placebo (after DeMots & Glasser 1989).

continuous and intermittent therapy with nitroglycerin 0.4 mg/h in a double-blind 2-week parallel study in 127 patients. Both continuous and intermittent therapy gave similar statistically significant improvement in exercise duration and time to ST-segment depression compared with baseline. Unfortunately, neither the duration of the patch-free period nor the timing of exercise testing was given in this brief report.

2.3 Phasic-Release Patches

A phasic-release nitroglycerin patch is being investigated which releases most of the dose in the first 12 hours and only 10 to 15% in the last 6 hours of each 24-hour period. Preliminary placebo-controlled trials in small numbers of patients (around 10 to 15) have indicated that the initial effects of a single dose (7.5 mg/24h) are significant until about 10 to 12 hours after application. Thereafter, a loss of effect occurs, a situation which is similar to conventional patches. During repeated daily patch application for up to 1 week some studies have shown no attenuation of the acute response (Bergbauer & Weber 1989; Krepp & Turpe 1989; Parker 1989; Weber et al. 1989), whereas others have shown some attenuation but not complete loss (Reiniger & Rudolph 1987; Schirnick & Reifart 1989). Clearly, more experience is required in larger numbers of patients treated longer term to determine the possible clinical advantages of phasic-release patches.

3. Therapeutic Use in Other Conditions

3.1 Unstable Angina

Transdermal nitroglycerin has been seen as a possible alternative to the use of intravenous nitroglycerin, which has been effective for the acute control of refractory unstable angina (for review see Sorkin et al. 1984). Lin and Flaherty (1985) found that it was generally possible to maintain control of unstable angina with transdermal nitroglycerin 0.2 to 1.6 mg/h after 10 patients had been stabilised with intravenous nitroglycerin. In a placebo-controlled trial in 18 patients with unstable angina refractory to β-blockers and/or calcium [illegible] agonists, Dahlstrøm et al. (1986) were able [illegible] tain a significant reduction in anginal [illegible] transdermal nitroglycerin 1 mg/h during [illegible] day of treatment but this effect was lost [illegible] second day. In a brief report, Mauri et al. [illegible] noted that transdermal nitroglycerin 0.4 [illegible] oral verapamil 320 mg/day appeared [illegible] fective in the control of 10 patients with [illegible] angina. On available evidence it is [illegible] determine the efficacy of transdermal nitro[illegible] in this setting.

3.2 Congestive Heart Failure

The haemodynamic effects of single dose [illegible] dermal nitroglycerin in patients with [illegible] heart failure are discussed in section [illegible] studies have performed haemodynamic [illegible] ing after the repeated daily use of [illegible] nitroglycerin continuously for 24 hours. [illegible] (1987) found no response or a markedly [illegible] response in 11 'nitrate-responders' with [illegible] dose of 5 mg/h compared with the [illegible] an initial dose of 5 mg/h on the [illegible] Sharpe and Coxon (1984) treated 10 [illegible] had initially responded to a low dose of [illegible] mal nitroglycerin 0.2 mg/h with the same daily dose for 3 months. After 3 months' treatment there was no statistically significant increase in exercise duration compared with baseline, although the haemodynamic response (improvement in stroke volume index and pulmonary capillary wedge pressure) was still statistically significant 4 hours after patch application, but was attenuated compared with the response after the first application. However, haemodynamic monitoring was not performed more than 4 hours after patch application with the final dose (i.e. only the peak effect was measured).

Sharpe et al. (1987) selected 8 of 10 patients with congestive heart failure who initially responded to a single dose of transdermal nitroglycerin 0.4 mg/h. These patients were then randomised to receive 1 month's treatment with the same patch dose given intermittently (removed for 8 hours in each 24-hour

period) or continuously (for 24 hours each day) in a crossover manner. The acute haemodynamic response on the first day of treatment, which was statistically significant until about 4 hours after patch application, was not attenuated after 1 month of intermittent therapy, but was completely abolished with continuous therapy despite the acute haemodynamic response being measured 2 hours after patch removal (table I).

Lindvall et al. (1988) are the only investigators to have published a controlled trial that examined the signs and symptoms of congestive heart failure, as well as exercise testing and echocardiography, during long term continuous treatment of 18 patients with titrated doses of nitroglycerin 0.2 to 0.6 mg/h. In a double-blind, crossover study no statistically significant differences were seen between transdermal nitroglycerin and placebo after 4 weeks' treatment with respect to patient or investigator assessment of signs and symptoms, exercise testing or echocardiographic findings.

In conclusion, continuous patch treatment with nitroglycerin does not appear to be an effective long term treatment in patients with congestive heart failure. However, the preliminary results of Sharpe et al. (1987) would seem to indicate that intermittent therapy warrants further study.

3.3 Other Potential Therapeutic Uses

Verma et al. (1988) studied the effect of transdermal nitroglycerin 0.2 to 1.6 mg/h up to 4 hours after patch administration to 67 patients with acute myocardial infarction. Systemic arterial blood pressure was reduced, resulting in a slight increase in heart rate in patients with normal left ventricular function but not in those with acute heart failure. Systemic vascular resistance was reduced, while left heart filling pressure was lowered only in those patients with acute heart failure. Cardiac stroke work was reduced only in those without acute heart failure, and cardiac index was unaffected in patients with or without acute heart failure.

A preliminary study of transdermal nitroglycerin 0.4 mg/h in 10 patients with pulmonary hypertension indicated a significant beneficial haemodynamic response (reductions in pulmonary artery, pulmonary capillary wedge and right atrial pressures, and pulmonary vascular resistance), although significant attenuation occurred after the first 12 to 14 hours (Daum & Heinl 1986). During continuous treatment for 4 weeks with the same dose, a significant response was still seen up to 6 hours after patch application.

In 11 patients with hypertension not controlled

Table I. Mean maximal haemodynamic changes (2 to 3 hours after patch application) occurring after an initial 0.4 mg/h dose of transdermal nitroglycerin and after reapplication following 1 month of intermittent or continuous therapy (0.4 mg/h for 16 and 24 hours each day, respectively) in 8 patients with congestive heart failure (after Sharpe et al. 1987)

Haemodynamic variable	Mean value[a]					
	initial		intermittent		continuous	
	pre[b]	post[c]	pre[b]	post[c]	pre[b]	post[c]
Cardiac index (L/min/m²)	2.1	2.4*	2.0	2.4**	2.1	2.2
Stroke volume index (ml/m²)	30	35**	30	37***	30	30
Stroke work index (g · ml/m²)	33	37**	33	40***	33	33
Pulmonary capillary wedge pressure (mm Hg)	22	16**	23	16***	22	18

a Some data extrapolated from graphical presentation.
b Before patch application.
c Maximally changed value after patch application. With continuous therapy the response to patch application was measured 2 hours after removal of the previous patch.
Symbols: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ versus control.

by the combination of a β-blocker and a diuretic, addition of transdermal nitroglycerin up to 0.6 mg/h significantly reduced systolic blood pressure, particularly in patients with higher baseline values. Diastolic blood pressure and heart rate were unaffected (Simon et al. (1986).

Studies in limited numbers of patients suggest possible benefits in various other disorders. Low-dose transdermal nitroglycerin patches reduced the incidence of phlebitis and infusion failure when applied close to venous cannulation sites (Khawaja et al. 1988, 1989; Wright et al. 1985). The drug was more effective than placebo in restoring erection and satisfactory sexual function in 26 impotent men (Claes & Baert 1989), and it was suggested in a pilot study that long term treatment with transdermal nitroglycerin 0.4 mg/h improved oesophageal achalasia (Bassotti et al. 1988). Khawaja and Weaver (1988) noted that an improvement in symptoms of serious distal limb ischaemia after the application of a 0.4 mg/h nitroglycerin patch to the dorsum of the foot was a useful predictor of a good response to subsequent lumbar sympathectomy. Studies in limited numbers of patients with Raynaud's phenomenon have indicated conflicting results after 2 to 3 weeks' treatment with a low dose of transdermal nitroglycerin: Sovijärvi et al. (1984) found no beneficial effect whereas Nahir et al. (1986) found a significant positive response.

In none of these areas is there sufficient evidence to advocate routine use of transdermal nitroglycerin.

4. Adverse Effects

Adverse effects associated with the use of nitroglycerin have been recognised and well characterised for over 100 years (for review see Abrams 1983; Elkayam & Aronow 1982; Frishman 1985). Nitroglycerin is usually well tolerated and when adverse effects do occur they may be controlled by dosage reduction, with discontinuation of therapy rarely being required. Most adverse effects are directly linked to the vasodilatory properties of nitroglycerin.

Headache of variable intensity is the commonest effect. It is usually attenuated after several days' continuous therapy, and may be treated by dosage reduction or with the use of mild analgesics [illegible]

The next most frequent adverse effect [illegible] tural hypotension, giving rise to dizziness, [illegible]ness and even syncope. The hypotension [illegible] sultant reflex tachycardia may reduce [illegible] perfusion pressure and worsen anginal [illegible] Bradycardia has been reported in some [illegible] with acute myocardial infarction. Other [illegible] quently reported adverse effects include [illegible] nausea and vomiting.

There is little reason to believe that the adverse effect profile of nitroglycerin is markedly [illegible] during the use of patches compared with its delivery via other dosage forms, with the exception of some adverse effects which are specifically [illegible]tioned here. Olivari and Cohn (1983) noted a [illegible] than normal incidence of gastrointestinal [illegible] effects during the use of patches in healthy [illegible]teers, although no subsequent studies [illegible] marked on this. Transdermal nitroglycerin [illegible] have been associated with a number of [illegible] reactions, mostly mild transient erythema [illegible] contact site. This is also frequently [illegible] use of placebo patches. However, case reports [illegible] been published of reversible macular erythema[illegible] lesions, which are usually mild but occasionally severe (Apted 1988; Carmichael & Foulds 1989; Di Landro et al. 1989; Fischer & Tyler 1985; Letendre et al. 1984; Rosenfeld & White 1984; Topaz & Abraham 1987; Weickel & Frosch 1986). Nitroglycerin itself was usually the causative agent, although one report proved that the delivery system (some component of the patch or excipient) was responsible (Letendre et al. 1984). Lastly, nitroglycerin patches should be removed before elective cardioversion or defibrillation because arcing may occur if the electrode overlies a patch (Babka 1983).

Some indications of the tolerability of nitroglycerin patches in general practice have been provided by postmarketing surveillance studies involving tens of thousands of patients usually treated with low dosages (0.2 to 0.4 mg/h) for up to 3 months (Agabiti Rosei et al. 1987; Bridgman et al. 1984; Letzel & Johnson 1983, 1984; Strano et al.

1990; Tattersall et al. 1985). Adverse effects occurred in about 20 to 30% of patients and led to treatment withdrawal in about 5 to 10% of patients. Headache, mostly occurring within the first few days of treatment, accounted for about three-quarters of all adverse effects and of withdrawals due to adverse effects. Cutaneous reactions were the next most frequent unwanted effect, occurring in about 2 to 4% of patients and leading to withdrawal of treatment in about half of these.

Some studies have attempted to compare the tolerability, in particular local tolerability, of different, clearly specified formulations of nitroglycerin patches in healthy volunteers or patients with angina. De Ponti et al. (1989) found no difference in the tolerability of Adestrin® (equivalent to Deponit®), Nitroderm® and Nitro-Dur®. Two studies showed no significant difference in tolerability between Nitrodisc® and Transderm-Nitro® (Cronin et al. 1987; Schrader et al. 1986), while another study (Rayment et al. 1985) noted that Transderm-Nitro® appeared to be better tolerated than Nitrodisc®.

5. *Drug Interactions*

Clinically relevant drug interactions have not been observed during the use of nitroglycerin patches, although this is not an area which has been specifically investigated. Drug interactions may occur during other methods of nitroglycerin administration (Elkayam & Aronow 1982). Phenobarbital (phenobarbitone) may enhance the metabolism of nitroglycerin and lower plasma concentrations, but this probably has no effect on the haemodynamic response. Alcohol may inhibit nitroglycerin metabolism and enhance its activity. Nitroglycerin can potentiate the hypotensive effect of tricyclic antidepressants and may retard the catabolism of opioids. Indomethacin may inhibit the peripheral vasodilatory effect of nitrates.

6. *Dosage and Administration*

The suggested starting dose of transdermal nitroglycerin in patients with angina is between 0.2 and 0.4 mg/h. Doses between 0.4 and 0.8 mg/h have shown continued effectiveness for 10 to 12 hours/day for at least one month of intermittent administration. Although the minimum nitrate-free interval has not been defined, a nitrate-free interval of 10 to 12 hours appears sufficient. Thus, an appropriate dosing schedule for nitroglycerin patches would include a daily 'patch-on' period of 12 to 14 hours and a daily 'patch-off' period of 10 to 12 hours. In most patients the patch-free interval should be at night. It should be noted that results of a controlled clinical trial suggest that exercise tolerance may be decreased at the end of the patch-free interval. Patients should be monitored for a possible increase in the incidence of angina in the hours prior to patch application.

The patch or patches can be applied to any skin surface except the distal parts of the extremities; the usual sites are the chest or upper arm. If hair interferes with patch adhesion, then the area should be clipped (not shaved) before application. Subsequent applications should be made to different skin areas.

The drug is contraindicated in patients with known nitrate intolerance or marked anaemia.

Treatment should be withdrawn gradually to avoid the risk of any rebound phenomenon.

7. *Place of Transdermal Nitroglycerin in Therapy*

Nitrates as a group have been used extensively to treat patients with stable angina. The transdermal nitroglycerin patch has been seen as a convenient method of drug delivery, and there are many different brands available worldwide. Certain patches may offer advantages in terms of better patch adhesion or cosmetic acceptability, but all seem to be regarded as therapeutically equivalent for both efficacy and safety.

Tolerance to the anti-ischaemic and antianginal effects of nitrates is a recognised therapeutic problem which unfortunately appears to occur in the majority of patients treated with continuous 24-hour application of nitroglycerin patches. As constant 24-hour plasma concentrations are not desirable, alternative approaches to therapy are needed.

To maximise the therapeutic effect and avoid tolerance, intermittent therapy is advocated. Removing the patches for 10 to 12 hours in the evening and applying new ones in the morning allows plasma nitroglycerin concentrations to drop during the night, when most patients experience few angina attacks. However, this approach ensures that nitroglycerin is present in the systemic circulation and exerting antianginal effects in the period before the early morning peak of attacks.

Comparisons with continuous therapy show the intermittent regimen to have a relatively low level of tolerance development. One study found a decreased exercise capacity to angina onset with long term intermittent therapy prior to patch application compared with placebo, which raised the possibility of a rebound phenomenon. Until further clarification, patients should be monitored carefully for increased angina frequency or severity during the patch-free period of intermittent therapy.

The therapeutic value of nitroglycerin patches in patients with disease states other than angina (e.g. Raynaud's phenomenon, unstable angina) cannot be determined on present information. In congestive heart failure, particularly, continuous patch application does not appear effective. The value of intermittent therapy is also uncertain despite the positive findings of a very small study, but warrants further investigation.

In conclusion, the place of nitroglycerin patches in the therapy of angina remains to be clarified by further well designed studies comparing this treatment with other therapeutic options. However, it appears that this convenient and cosmetically acceptable dosage form may have potential utility if administered in an intermittent regimen providing daily patch-free periods to reduce the development of tolerance.

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Correspondence: *Karen L. Goa*, Adis International Limited, 41 Centorian Drive, Private Bag, Mairangi Bay, Auckland 10, New Zealand.